

REMARKS

Claims 2, 4, 6, 12, 16 and 19-31 are pending in the present application. Claims 2, 4, 12, 16, and 19 have been amended without prejudice and without acquiescence. Claims 32-40 have been added. Support for claims 35-40 can be found on page 4. Support for claims 32-24 can be found on the bottom of page 8 through the top of page 9. Support for the term “reagents” can be found throughout the specification, for example, on page 10, lines 21-27. Support for the term “moving” can be found throughout the specification, for example, page 2, lines 25-30, page 5, line 32 to page 6, line 8 and Figure 1. No new matter has been added.

The issues outstanding in this application are as follows:

- Claims 2, 20 and 21 were rejected under 35 U.S.C. § 102(b) as being anticipated by Ronaghi et al. (Anal. Biochemistry, 1996).
- Claims 2, 4, 6, 12, 16 and 19-31 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Ronaghi et al., in view of Mian et al., (US 6,319,469).
- Claims 2, 6, 12, 19, 20-22, 27, 28 and 30 were rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.
- Claims 2, 4, 6, 12, 16 and 19-31 were rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described.
- Claims 12 and 16 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement rejection.

Applicants respectfully traverse the outstanding rejections, and Applicants respectfully request reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. 35 U.S.C. § 102(b)

Claims 2, 20 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ronaghi et al. (*Anal. Biochemistry*, 1996). The Action states that Ronaghi et al. teaches the methods of using a microfluidic device to determine a nucleotide base in a nucleic acid sample. Applicants respectfully traverse.

Anticipation of a claim is only established where “each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

The teachings employed by Ronaghi et al. does not anticipate the claims found in the present application. The Examiner erroneously construes the meaning of “microfluidic device” to mean any suitable device which holds liquids on a microliter scale. Applicants contend that it is well known to those of skill in the art that the term “microfluidics” and “microfluidic device” refer to a device in which there is a transport of liquid. Applicants refer the Examiner to passages of the present application that discusses microfluidic devices (see page 5, line 32 to page 6, line 8 and Figure 1). The microfluidic devices discussed require transport of sample, reagents and the like by the use of liquid flow, e.g., from a sample loading or application area to one or more reaction chambers and a detection chamber.

In order to advance the prosecution of the present application, Applicants have amended independent claim 2 without prejudice and without acquiescence to indicate that fluids are moved within the microchannel structure, which is not taught by Ronaghi et al. Thus, in light of this amendment Applicants respectfully request that the rejection be withdrawn.

II. 35 U.S.C. § 103(a)

Claims 2, 4, 6, 12, 16 and 19-31 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ronaghi et al. in view of Mian et al., (US 6,319,469). The Action states that Ronaghi et al. teaches a method of identifying a sequence of a portion of DNA, but does not teach identifying a sequence of a portion of DNA using a microfluidic device. The

Action further states that Mian et al. teaches the use of a microfluidic device for the method of Ronaghi et al. Applicants respectfully traverse.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicants contend that neither Ronaghi et al. nor Mian et al. alone or in combination teaches and/or suggests the present invention. Ronaghi et al. teaches sequencing using a stepwise addition of various nucleotides that are added or not added to an extending primer. Mian et al. teaches DNA sequencing in Example 7 (column 48-column 49). The DNA sequencing taught by Mian et al. is enzymatic sequencing by the Sanger method, which comprises extending the primer in simultaneous presence of all four nucleotides and trace amounts of a fluorescently labelled dideoxynucleotide, and ultimately uses electrophoresis to separate the dideoxynucleotide-terminated DNA fragments so that the sequence is determined by the fluorescent pattern of the DNA fragments. Thus, Applicants assert that the sequencing methods of Mian et al. and Ronaghi et al. are not similar and one of skill in the art would not combine the references.

For example, in Example 7 of Mian et al., the DNA polymerase reaction is carried out on a disc as one step in a mixture containing DNA polymerase, template DNA (sample DNA), primer DNA, all the four different deoxynucleotides in unlabelled form and a terminator in the form of a fluorescently labelled dideoxynucleotide. The reaction mixture is spun after the polymerase reaction to an electrophoresis unit on the same disc to fractionate the mixture into fractions each of which contains extended primers of a certain length that differ between the fractions. This method is completely different than the method described by Rongahi et al. in that neither the sample DNA nor the primer DNA of Mian et al. are immobilized to a surface of the reaction chamber prior to the polymerase reaction. Ronaghi et al. teaches that the sample DNA is first immobilized to a solid support and then the polymerase reaction is carried out in a repetitive mode as discrete steps of addition of each nucleotide (See first column of page 85, paragraph entitled *Real-Time Sequencing*). Thus, Mian et al. does not teach immobilization of DNA for sequencing and Ronaghi et al. teaches immobilization of DNA for sequencing; these teachings are opposite of one another. Thus, Applicants assert that claims 2, 4, 6, 12, 16 and 19-31 are not *prima facie* obvious because it

is improper to combine references that teach away from the asserted combination. *In re Haruna*, 249 F.3d 1327, 58 USPQ2d 1517 (Fed. Cir. 2001); *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). “A reference may be said to teach away when a person of ordinary skill, upon reading the reference....would be led in a direction divergent from the path that was taken by the applicant.” *Tec air, Inc. v. Denso Mfg. Mich. Inc.*, 195 F.3d 1353, 1360, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999).

Yet further, the Examiner appears to pick and choose elements from the various DNA procedures taught by Mian et al. as a suggestion to combine Ronaghi et al. and Mian et al. For example, the Examiner states “Example 3 which includes the incorporation of the fluorescently labeled DNA to one or more reaction areas so that extension of primer occurs as a result from complementarity of the added dideoxynucleotides with the strand of sample DNA that is part of the immobilized double stranded DNA”. Applicants traverse this statement. Neither Ronaghi et al nor the present invention utilizes labeled DNA. Dideoxynucleotides are not mentioned in Example 3. Applicants assert that at best Mian et al. may teach immobilized DNA, however, this teaching of immobilized DNA is not related to methods of DNA sequencing as taught by Ronaghi et al. The immobilized DNA taught in Mian et al. relates to determining the size of a DNA molecule and mutation detection; not the sequence of the DNA molecule as taught by Ronaghi et al. Another example, is that the Examiner asserts that column 47 of Mian et al. teaches washing or removing excess reagents. Applicants traverse this statement. The washing or removing step taught in column 47 relates to DNA preparative synthesis; not DNA analytical sequencing. Preparative synthesis of DNA means production and isolation of predetermined oligopeptides while sequencing means determination of the order of the bases in unknown DNA. These DNA reactions are completely different from one another. Applicants assert that the Examiner **can not** ‘pick and choose among the individual elements of assorted prior art references to recreate the claimed invention,’ but rather, the Examiner must look for ‘some teaching or suggestion in the references to support their use in the particular claimed combination.’ *Symbol Technologies, Inc. V. Opticon, Inc.*, 935 F.2d 1569, 19 USPQ2d 1241 (Fed. Cir. 1991).

Yet further, Applicants submit that this rejection is an application of an “obvious to try” standard in the field of molecular biology and microfluidics. The “obvious to try” standard has been held to constitute an improper ground for a 35 U.S.C. § 103 rejection, for example *In re O’Farrell*, 858, F.2d 894, 903 (Fed. Cir. 1988). Applicants respectfully submit

that in the area of molecular biology, while it is often obvious for one of ordinary skill in the art to search for a solution, the actual solution is rarely, if ever, obvious. Applicants contend that until the present invention, “real-time DNA sequencing” had not been performed in a microfluidic device.

Thus, with the lack of teaching or suggestion to design a microfluidic apparatus that is capable of immobilizing DNA molecules, moving liquids and performing cycles of sequencing reactions in which each cycle is represented by a separate step comprising addition of deoxynucleotide, deoxynucleotide analogue or a dideoxynucleotide to a nucleic acid molecule, Applicants assert that the references do not meet the basic requirements of a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit reconsideration and withdrawal of the outstanding rejection under 35 U.S.C. 103(a) as being unpatentable over Ronaghi et al. in view of Mian et al.

III. 35 U.S.C. § 112, second paragraph rejection

Claims 2, 6, 12, 19, 20-22, 27, 28 and 30 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse.

A. Claims 19, 27, 28, and 30.

Claims 19, 27, 28, and 30 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse.

In order to advance the prosecution of the present application, Applicants have amended claim 30 without prejudice and without acquiescence to correct the antecedent basis. Thus, in light of this amendment, the rejection is moot and Applicants respectfully request that the rejection be withdrawn.

B. Claims 2, 6, 12, and 20-22.

Claims 2, 6, 12, and 20-22 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse.

In order to advance the prosecution of the present application, Applicants have amended independent claim 2 without prejudice and without acquiescence to clarify the

scope of the present invention. Applicants assert that one of skill in the art recognizes that in order for DNA extension to occur there is a free part of one of the DNA strands. Applicants remind the Examiner that “the requirement that the claims ‘particularly point [] out and distinctly claim []’ the invention is met when a person experienced in the field of the invention would understand the scope of the subject matter that is patented when the claim is read in conjunction with the rest of the specification. ‘If the claims when read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.’ *Miles Laboratories, Inc. v. Shandon*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993)”. Thus, Applicants assert that one of skill in the art realizes that in the presence of a primer DNA that is hybridized to a sample DNA there is a free DNA end such that extension of the DNA can occur. Thus, in light of these amendments, Applicants respectfully request that the rejection be withdrawn.

IV. 35 U.S.C. § 112, first paragraph rejection

Claims 2, 4, 6, 12, 16, and 19-31 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in such a way as to reasonable convey to one skilled in the art that the inventors at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

A. Claims 2, 4, 6, 12, 16, and 19-31

Claims 2, 4, 6, 12, 16, and 19-31 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described. The Examiner states that the limitation of “removing pyrophosphate, DNA polymerase...or dideoxynucleotide” in claims 2, 4, and 19 appears to be new matter. Applicants respectfully traverse.

The fundamental inquiry is whether the material added by amendment was inherently contained in the original application. *Vas Cath Inc. v. Mahurkar*, 932 F.2d 1555, 1563, 19 USPQ2d 111, 1116 (Fed. Cir. 1991).

The Examiner also states that basis was found on page 2 and page 8 for the inclusion of a step that removes or washes excess deoxynucleotide or deoxynucleotide analogue, but no basis for the other elements. Applicants are confused by this generalization. Page 2, line 2 of the specification states “solution is removed from the well”. Page 8, line 3, states a washing

step, it does not mention that only deoxynucleotide or deoxynucleotide analogues are removed. Applicants assert that pyrophosphate, DNA polymerase, deoxynucleotide or deoxynucleotide analogs or dideoxynucleotides are all soluble reagents that would be considered a “solution” or “liquid” that would be removed. Applicants direct the Examiner’s attention to page 9, lines 1-5 which states “the washing step solves the problem with loading the reaction mixes to one well many times and thereby getting a larger and larger volume.” Page 10, lines 20-23 states that the reaction mix may include at least nucleotide (deoxy- or dideoxy), polymerase, luciferin, APS, ATP sulphurlase and luciferase. Thus, Applicants assert that all the elements have basis in the specification.

However, in order to advance the prosecution of the present application, Applicants have amended independent claims 2, 4, and 19 without prejudice and without acquiescence to clarify the scope of the present invention to indicate that reagents are removed. Yet further, Applicants have amendment claims 12 and 16 without prejudice and without acquiescence to recite “centripetal”. Thus, in light of these amendments, Applicants respectfully request that the rejection be withdrawn.

B. Claims 12 and 16

Claims 12 and are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. Applicants respectfully traverse.

In order to advance the prosecution of the present application, Applicants have amended claims 12 and 16 without prejudice and without acquiescence. Thus, in light of these amendments, Applicants assert that this rejection is moot and respectfully request that the rejection be withdrawn.

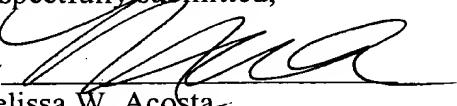
CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02216US0 from which the undersigned is authorized to draw.

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Respectfully submitted,

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